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USPT,PGPB,JPAB,EPAB,DWPI	11 and (thrombocytopenic purpura) or (hemolytic uremi\$ n)	55	<u>L2</u>
USPT,PGPB,JPAB,EPAB,DWPI	(protein adj C)	4435	<u>L1</u>

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L2: Entry 25 of 55

File: USPT

Nov 23, 1999

DOCUMENT-IDENTIFIER: US 5990079 A

TITLE: Agents affecting thrombosis and hemostasis

**BSPR:**

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. After initiation of clotting, blood coagulation proceeds through the sequential activation of certain plasma proenzymes to their enzyme forms. These plasma glycoproteins, including Factor XII, Factor XI, Factor IX, Factor X, Factor VII, and prothrombin, are zymogens of serine proteases. Most of these blood clotting enzymes are effective on a physiological scale only when assembled in complexes on membrane surfaces with protein cofactors such as Factor VIII and Factor V. Other blood factors modulate and localize clot formation, or dissolve blood clots. Activated protein C is a specific enzyme that inactivates procoagulant components. Calcium ions are involved in many of the component reactions. Blood coagulation follows either the intrinsic pathway, where all of the protein components are present in blood, or the extrinsic pathway, where the cell-membrane protein tissue factor plays a critical role. Clot formation occurs when fibrinogen is cleaved by thrombin to form fibrin. Blood clots are composed of activated platelets and fibrin.

**BSPR:**

The amino acid sequences and genes of most of the plasma proteins involved in hemostasis of blood have been determined, including Factor VIIa, Factor IXa, Activated Protein C, Factor X and Factor Xa. FIG. 1 shows the complete sequence of the precursor form of Factor X as described by Davie, E. W., in Hemostasis and Thrombosis, Second Edition, R. W. Coleman et al. eds. (1987) p. 250. Factor X is a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family, which also includes Factors VII and IX, prothrombin, protein C and protein S (Furie, B., et al., Cell (1988) 53:505).

**BSPR:**

The most common forms of hemophilia are hemophilia A which reflects a deficiency in the functioning of Factor VII, and hemophilia B which reflects a deficiency in the functioning of Factor IX (also known as Christmas factor). These forms of hemophilia are well known. Similarly, other patients are treated currently for deficiencies of other blood factors (VII, X, XI, XIII) or von Willebrand's disease. Factor VII deficiency is not as clinically well-defined as hemophilia A or B, however patients with Factor VII deficiency have been reported to have extensive bleeding. Protein C deficiency is associated with thrombotic risk.

**BSPR:**

Factor Xa, and several other activated blood factors, have not heretofore been useful as pharmaceuticals because of their extremely short half-life in serum, which for example typically is only about 30 seconds for Factor Xa. In the invention described below, the half-life of these agents in serum is extended by providing a transiently inactivated, slow release form, preferably an acylated form. In certain embodiments relating to Factor X, an acyl group is bound to the serine at the active site and inhibits clearance and is only slowly hydrolyzed to generate the active form of Factor Xa. In similar fashion, this invention also relates to other transiently inactivated blood factors, including activated Protein C, Factor IXa and Factor VIIa.

**BSPR:**

The therapeutic materials of the invention are inactive (either permanently or transiently) forms of mammalian blood factors including Factor IXa, Factor VIIa, activated Protein C, and Factor Xa.

**BSPR:**

Other aspects of the invention include pharmaceutical compositions of the therapeutically useful Factor Xa proteins and to methods to prevent or treat thrombosis or other pathological events initiated by thrombin using these compositions. In

certain other aspects of this invention, transiently inactivated blood proteins such as activated Protein C are used as antithrombotics, where controlled, slow-release formulations are desired.

DRPR:

FIG. 14 shows the activation of acyl activated protein C.

DEPR:

"Factor IX", "Factor VII" and "activated Protein C" refer to the respective native or recombinantly produced protein sequence as commonly known.

DEPR:

"Blood factor" refers to blood coagulation factors generally, and preferably to a group of blood factors including Factor X, Factor VII, Factor IX, and Protein C, in their inactive, active, or inactivated active forms.

DEPR:

The genomic organization and coding sequence for human Factor X are known and the cDNA has been retrieved and sequenced (Leytus, S. P., et al., Proc Natl Acad Sci USA (1984) 81:3699; Kaul, R. K., et al., Gene 1(1986) 41:311-314). The complete Factor X cDNA sequence is shown in FIG. 4. Full length sequences for other blood factors such as thrombin, Factors IXa and VIIa, and activated Protein C are well known in the field. Throughout this specification, techniques described in relation to Factor X-related polypeptides are fully applicable to the other blood factors claimed in this invention, and are provided for exemplary purposes only.

DEPR:

Certain preferred aspects of this invention relate to transiently inactivated blood factors, such as Factors VIIa, IXa, Xa, and activated Protein C. Transient inactivation may be accomplished by a variety of methods, including binding of an antibody/antibody fragment to the active region, binding of moiety which blocks sterically the proteolytic or other active domain, or incorporation of a chemical moiety which blocks the active blood factor domain and gradually is released from the blood factor. Particularly preferred embodiments of this invention are blood factor polypeptides which are transiently inactivated by being acylated.

DEPR:

The acylated polypeptides of this invention, such as AcXa, AcIXa, AcVIIa, and Acylated activated Protein C, are prepared by standard acylation reaction of the corresponding blood factor, whether recombinantly produced or isolated from plasma, according to procedures analogous to those set forth, for example, or referenced in Cassels, R. et al. Biochem J (1987) 247:395-400 or U.S. Pat. No. 4,337,244 cited above.

DEPR:

The Factor Xai peptides of the invention are prothrombinase inhibitors and are thus useful in procedures complicated by thrombosis and in conditions whose pathogenesis involves thrombin generation. These conditions include those involving arterial thrombosis, such as unstable (i.e., rest) angina and abrupt vessel closure during vascular interventions including coronary and peripheral angioplasty and atherectomy, and during and after vascular bypass procedures (peripheral and coronary), reocclusion after thrombolytic therapy for myocardial infarction, thrombotic stroke (stroke in evolution), and thrombosis due to vasculitis (Kawasaki's disease). Also included are conditions involving venous thrombosis, such as deep venous thrombosis of the lower extremities, pulmonary embolism, renal vein, hepatic vein, inferior vena cava thrombosis, and cavernous sinus thrombosis. Other target conditions are those involving diffuse activation of the coagulation system, such as sepsis with disseminated intravascular coagulation, disseminated intravascular coagulation in other settings, thrombotic thrombocytopenic purpura, and rare conditions of unknown etiology (Lupus anticoagulant).

DEPR:

The transiently inactivated activated Protein C polypeptides of this invention are useful as antithrombotics. The transiently inactivated Factors IXa, Xa, and VIIa of this invention are useful hemostatic factors, particularly for the treatment of hemophilia as replacement or bypass factors. The modified blood factors of this invention, modified to extend their half-life in vivo, are useful in treating hemophilia whether the origin of the hemophilia resides in the Factor X, IX, or VII gene, or the more widespread types, hemophilias A and B.

DEPR:

Activation of acyl activated protein C is shown in FIG. 14. Acylated aPC prepared as described above was incubated in a buffer at pH 7.5 at room temperature. Over the time course of experimentation, withdrawn aliquots are assayed for aPC activity in a chromogenic assay. A sample of unmodified human aPC was subjected to the same incubation protocol. FIG. 14 depicts the relative percent activity in incubated acyl aPC versus control aPC.